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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)	
Office Action Summary	09/783,083	DUKLER ET AL.	
File Applicant Copy	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-58 and 64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-58 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Please note: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1639.

Please note: The Examiner respectfully asks Applicants for a clean copy of all pending claims.

Status of the Application

1. The Response filed January 19, 2003 (Paper No. 9) is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-29 and 59-63 were cancelled, claim 64 was added and claims 30, 32, 34, 38, 40, 45 and 52-55 and 57-58 were amended.

4. Therefore, claims 30-58 and 64 are examined on the merits in this action.

Information Disclosure Statement

5. The information disclosure statement filed December 4, 2002 (Paper No. 4), fails, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because several publications cited therein lack publication dates, title, author, and/or relevant pages, which are necessary elements for consideration e.g., marked DL, FC, QL. While the other patent and other

publications cited therein, and supplied, therewith, have been considered as to the merits, these three publications have not. Applicant is advised that the date of any re-submission of these citations contained in this information disclosure statement or the submission of the missing element – their publication dates – will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 C(1).

Withdrawn Objections/Rejections

6. With respect to the rejections under the second paragraph of 35 U.S.C. 112, the rejections with regard to terms "harmless" and "representation" (see Paper No. 6, paragraphs 14-15) are withdrawn in view of Applicants' amendments and/or arguments. The rejection under 35 U.S.C. § 103(a) with regard to Liang et al, Seitz et al and Seifert et al is withdrawn in view of Applicants' amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112 – Maintained Rejection

7. Claims 30-58 and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the limited number of complex carbohydrate libraries disclosed, does not reasonably provide enablement for ***any*** complex carbohydrate library, which claim 1 literally encompasses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The scope of claim 1 encompasses complex carbohydrate libraries with carbohydrate members that are unbounded by the number of

saccharide subunits, substituents or the degree and type of linkages between saccharide units or saccharide units and other substitutents. Furthermore, claim 1 encompasses complex carbohydrate libraries, which contain carbohydrate members that have yet to be prepared or envisioned. Furthermore, claim 1 encompasses complex carbohydrate libraries, which contain unusual or unnatural sugars as substrates, which may not be good substrates for the enzymes disclosed by applicant. Consequently, the examples set forth in the specification do not constitute support for the entire scope of claim 1 and, as a result, the entire scope of claim 1 could not be supported without undue experimentation.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Claim 1 is drawn to a method comprising the steps of "producing an addressable combinatorial complex carbohydrate library." Such a claim represents a broad scope because it reads on all possible complex carbohydrates (even ones that have yet to be synthesized) including

complex carbohydrate libraries that contain unusual or unnatural sugars, which may not be good substrates for the enzymes disclosed by applicant.

(3 and 5) The state of the prior art and the level of predictability in the art:

According to the applicants, "[a]lthough carbohydrate libraries of limited complexity have been synthesized using various chemical methods, a combinatorial library of complex carbohydrates with a high rank of structural complexity resembling natural complex carbohydrates (e.g., highly branched structures) has not yet been produced" (see page 10 of specification, lines 11-15). The applicants further state that "the unavailability of an efficient and comprehensive synthesis method applicable for producing diverse and complex carbohydrate species" has led to a lag in discovering new carbohydrate-derived pharmaceutical reagents (see page 14 of specification, lines 16-20). Consequently, the state of the prior art does not provide adequate guidance for one of skill in the art to predict how to synthesize ***any*** complex combinatorial carbohydrate library (especially those libraries not disclosed by the applicants) without undue experimentation especially libraries that contain unusual or unnatural sugars.

Furthermore, the use of enzymes in synthetic reactions are inherently "unpredictable" because unpredictable steric effects often prevent the desired enzymatic reaction. For example, applicant verified the β-1,4-galactosyltransferase mediated addition of β-D-galactose to "the plate immobilized phenyl-β-D-GlcNAc" using a 22 atom linker, but was not able to detect any transfer of β-D-galactose to "the plate immobilized β-D-GlcNAc" using a 20 atom linker. The applicant "suggested" that the differences in reactivity were caused by the small change in "linker length" i.e., 22 to 20 atoms, which clearly

demonstrates the "unpredictable" nature of these enzymatic reactions (see page 81, lines 13-19). Furthermore, applicant acknowledges this limitation and others by stating that the "linker length, flexibility of the complex carbohydrate, immobilization of carbohydrate groups and steric hinderance are also important factors effecting synthesis efficiency" (see page 87, lines 4-6).

(4) The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. Such persons of ordinary skill in this art, given its unpredictability (see above), would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have only provided a limited number of working examples describing complex carbohydrate libraries that would not adequately instruct one of ordinary skill in the art to synthesize ***every*** complex carbohydrate library. Furthermore, applicant has not provided any examples of complex carbohydrate libraries with unnatural sugars, which may not be good substrates for the enzymes disclosed by applicant.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The quantity of experimentation needed to make or use the claimed invention would be great. The art is inherently unpredictable (see above). The preparation of the complex carbohydrate libraries is unpredictable because there is no general glycosylation methodology for the preparation of linked saccharide units that proceeds quantitatively and stereospecifically. Furthermore, the list of enzymes provided

by applicant would not provide for a means to synthesize ***all*** complex carbohydrates. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. (See *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991)). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response to Arguments

8. Applicant's arguments have been fully considered but they are not found persuasive. The Examiner's rationale is set forth below.

The Examiner concedes all of the arguments listed on pages 4-11 of Paper No. 9 with regard to the 35 USC § 112, first paragraph (i.e., the Enablement Rejection) with the exception of the following:

Applicants argue that "[i]t will be appreciated that not all unusual or unnatural sugars are less efficient substrates for enzymatic reactions. In fact some modified or unnatural chemical derivatives of those sugars are better, more accessible substrates and as such are preferred in synthesis of complex carbohydrates. For example, the activity of the human enzyme β Gal-T1 towards GlcNAc is one order of magnitude lower then its activity towards p-Nitrophenylβ-

GlcNAc, a non-natural, chemical derivative of GlcNAc (See Table 1 of Amado et al. J.B.C. Vol. 273 No. 21 pp. 12770-12778 1998)" (see Paper No. 9, page 11, paragraph 2).

The Examiner contends that Applicants are not enabled for the synthesis of unusual or unnatural sugars that may not be good substrates for the enzymatic synthesis reaction because Applicants have not provided enough examples (i.e., Applicants provide one example above for β Gal-T1) and/or a general strategy to teach one of skill in the art how to use enzymes to synthesize ***all*** unnatural or unusual sugars. The following reference (i.e., Sears et al, see below) is put forth by the Examiner for the sole purpose of rebutting Applicant's argument (i.e., the argument shown above), which was published in 2002 to show that Applicants could not have been enabled for the full scope of their claims as of their filing date because Sears et al states that not all or even a significant portion of the unusual or unnatural sugars could be made as of 2002, which is after Applicants filing date.

For example, Sears et al states "[a]nother drawback of the enzymatic approach is that while enzymes are excellent at catalyzing the synthesis of natural products, their ability to accept novel saccharides with unusual or unnatural sugars as substrates may be poor; at best, it will be unknown. Models for the substrate preferences of glycosyltransferases are currently unavailable, and alteration of their specificity using protein engineering has experienced limited success" (see Sears, P.; Wong, C. -H. 'Strategies for Creating the Diversity of Oligosaccharides' In: Handbook of Combinatorial Chemistry Edited by K. C. Nicolaou et al. Weinheim: Wiley-VCH, 2002, Vol. 2, p. 713).

Applicant's further argue that "[c]omplex carbohydrate structures that currently not found in nature (i.e., non-naturally occurring carbohydrates) can include slight or large modifications to

naturally occurring complex carbohydrate structures or can be generated according to a predetermined design consideration. In any case, synthesis of non-naturally occurring complex carbohydrate structures is not more complicated than that of naturally occurring complex carbohydrate structures since such synthesis follows similar synthesis considerations. In fact, it is conceivable that in some cases, non-naturally occurring complex carbohydrate structures would be easier to generate than naturally occurring complex carbohydrate structures since non-naturally occurring complex carbohydrate structures can be designed while considering the types of enzymes and reactions needed."

The Examiner's position is that non-natural occurring carbohydrates would NOT on average be more easily synthesized than naturally occurring complex carbohydrates because the both methods would depend on naturally occurring enzymes, which would favor naturally occurring complex carbohydrates, especially in situation wherein the enzyme substrate represents a non-natural carbohydrate (see above) and thus applicants are not enabled for all non-naturally occurring complex carbohydrates. Furthermore, it is not clear to what extent the structure of a "non-naturally occurring" carbohydrate may vary from a "naturally occurring" carbohydrate and thus it is not even clear to what extent applicants would have to demonstrate that they are enabled to encompass the full scope of their claims (see 35 USC 112, second paragraph rejection below).

35 USC § 112, second paragraph – Maintained Rejection

9. Claims 30-58 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. For **claim 30**, the term "complex carbohydrate" is a relative term, which renders the claim indefinite. The term "complex carbohydrate" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, the applicants have not disclosed the number of monomers, the amount of branching, or the type of linkages that would be required for an oligomer to be classified as a "complex carbohydrate." Furthermore, the specification does not provide a standard for ascertaining these limitations because according to Figures 2 and 3, a complex carbohydrate may contain any number of monomers and any number of branch points (there are entries in the CarbBank database showing single monomer complex carbohydrates with no branch points). Therefore, it is not possible to determine the metes and bounds of the invention as claimed. Consequently, claim 30 and all dependent claims i.e., 31-58 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Response to Arguments

11. Applicant's arguments have been fully considered but they are not found persuasive. The examiner's rationale is set forth below.

Applicants argue that "the phrase "complex carbohydrate" is "not only an art recognized term, which defines a polysaccharide (branched or not), i.e., a molecule which includes at least two covalently attached saccharide monomers, but it is also defined in both scientific literature and dictionaries. "Complex carbohydrate" is in fact the name of the first text book on complex carbohydrates (Nathan Sharon, Addison Wesley Publishing company, 1975, ISBN 0-201-07324)" (see Paper No. 9, page 12, paragraph 2).

These arguments were not found persuasive for the following reasons:

The Examiner contends that the literature does not provide a consistent definition for the term "complex carbohydrate" and, as a result, the metes and bounds of the claimed invention cannot be determined in light of the specification, which does not provide a clear definition for the term. The Examiner puts forth the following reference solely for the purpose of rebutting applicants' arguments that the term "complex carbohydrate" is an art-recognized term that is clearly defined in the literature. For example, Anderson et al (Anderson, H.; Lamb, M.; Mendelson, R.; Ocana, A. M.; Stephen, A. M.; O'Brien, H. T. "The Carbohydrate Controversy Persists" Carbohydrate News, Issue 1, 1995, 1-7) states that "[t]he term 'complex carbohydrate' ... is ... poorly defined and means different things for various countries and for different researchers" (see Anderson et al, page 2, paragraph 2).

Furthermore, even if assuming *arguendo* that the term "complex carbohydrate" is properly defined in the literature, the Examiner contends that the specification contradicts applicants' own definition and, as a result, the metes and bounds of the claimed invention could still not be determined in view of the specification. The following passage of the outstanding rejection is particularly relevant:

> Furthermore, the specification does not provide a standard for ascertaining these limitations because according to Figures 2 and 3, a complex carbohydrate may contain any number of monomers and any number of branch points (there are entries in the CarbBank database showing single monomer complex carbohydrates with no branch points).

For example, applicants "define" a complex carbohydrate in their previous response as "a polysaccharide (branched or not), i.e., a molecule which includes at least two covalently attached saccharide monomers" (see Paper No. 6, page 12, paragraph 3). However, applicants' specification contradicts this definition by providing examples of "complex carbohydrates" that have only one monomer (see specification, figures 2 and 3).

Claim Rejections - 35 USC § 103 - Maintained

12. Claims 30-34, 36-40, 44-51 and 53-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dower et al (US #5,770,358) (Date of Patent is **June 23, 1998**; Date of filing is **September 16, 1992**), in further view of Nicolaou et al (Nicolaou, K. C.; Watanabe, N.; Li, J.; Pastor, J.; Winssinger, N. "Solid-Phase Synthesis of Oligosaccharides: Construction of a Dodecasaccharide" *Angew. Chem. Int. Ed.*, **1998**, *37(11)*, 1559-1561), and in further view of Schuster et al (Schuster, M.; Wang, P.; Paulson, J. C.; Wong, C. H. "Solid-Phase Chemical-

Enzymatic Synthesis of Glycopeptides and Oligosaccharides" *J. Am. Chem. Soc.*, **1994**, *116*, 1135-1136).

For **claim 30**, Dower et al teaches "methods for synthesizing random oligomers [including complex carbohydrates], with particular emphasis on particle-based synthesis methods [i.e., solid-phase library]" (see Dower et al, column 1, lines 11-18), which reads on the preamble of claim 30 wherein a method of "producing an addressable combinatorial complex carbohydrate library" is disclosed. Furthermore, Dower et al teaches "random oligomers [that] are synthesized on solid support" and an "identifier tag", which may be "attached directly to the oligomer with or without an accompanying particle, to a linker attached to the oligomer, to the solid support upon which the oligomer is synthesized, etc." (see Dower et al, column 3, lines 14-15, and 21; see also column 3, lines 28-38; see also Glossary, column 6, paragraph 3, lines 30-31), which reads on the preamble and part (a) of claim 30 wherein the complex carbohydrate library is "addressable" having a "plurality of locations." Dower also teaches that the carbohydrate libraries can be synthesized on a solid-support as mentioned above (see Dower et al, column 3, line 15), which also reads on part (a) of claim 30. Dower also teaches that the carbohydrate libraries can be synthesized with enzymes (see Dower et al, column 1, line 17; and see also Glossary, column 6, paragraph 3, lines 27-31) (oligomers are "formed from the ... enzymatic addition of monomer subuits. Such oligomers include ... linear, cyclic, and branched polymers of ... polysaccharides") (emphasis added), which reads on part (b) of claim 30. Dower et al also teaches that the synthesis of complex

carbohydrates can occur on a single substrate like a chip (see Dower et al, see columns 2-3, bridging paragraph; see also column 12, paragraph 3).

Although Dower et al teaches every limitation of claim 30 (see above), Dower et al does not provide a specific example of a "complex carbohydrate library." Furthermore, Dower et al does not provide a specific example of an "enzyme" used to make the complex carbohydrate library.

Nicolaou et al teaches a specific example of a "complex" carbohydrate library containing branched dodecasaccharides (see Nicolaou et al, page 1560, figure 2) (showing the solid-phase synthesis of a branched dodecasaccharide), which reads on the preamble of claim 30 for producing a "complex" carbohydrate library. Furthermore, Schuster et al teaches a specific example of an enzyme used to link carbohydrates to a solid support (see Schuster et al, page 1136, scheme 1, reaction steps d-f).

For **claim 31**, Dower et al teaches that "the solid supports may be joined to the oligomers ... by means of one or more linker molecules" (see Dower et al, column 3, lines 38-30) (see also Dower et al, column 8, second to last paragraph) ("When bound to a solid support, the oligomer is usually attached by means of a linker").

For **claim 32**, Dower et al does not provide a specific example of a linker that includes at least covalently linked monomers. However, Nicolaou teaches a linker with at least two covalently linked monomers (see Nicolaou et al, page 1559, figure 1).

For **claim 33**, Dower et al teaches that "one can cleave the linker from the bead, producing tagged oligomer in solution" (see Dower et al, column 23, lines 11-12) (see also Dower et al, column 8, second to last paragraph).

For **claim 34**, Dower et al teaches that "one can cleave the linker from the bead, producing tagged oligomer in solution" (see Dower et al, column 23, lines 11-12) (see also Dower et al, column 8, second to last paragraph), which reads on claim 34 wherein "the linker is cleavable under condition that do not affect a structure of each of said plurality of complex carbohydrate structures" because Dower et al shows that tagged oligomers can be produced in solution. Furthermore, Nicolaou also teaches the cleavage of a linker under conditions that do not affect the structure of the complex carbohydrates i.e., Nicolaou uses a light cleavable linker (see Nicolaou et al, page 1560, scheme 2, last step).

For **claim 36**, Dower et al does not provide a specific example of a linker for a complex oligosaccharide library. However, Nicolaou teaches a photolabile linker containing an alkyl chain (i.e., methylene group) (see Nicolaou et al, page 1559, figure 1).

For **claim 37**, Dower et al does not provide a specific example of a linker for a complex oligosaccharide library that is at least 20 Angstroms long. However, Schuster teaches a linker with 6 glycine residues that is >20 Angstroms long (see Schuster et al, page 1136, scheme 1, compound 3a showing NH-(Gly_6)-NH linker).

For **claim 38**, Dower et al teaches "one can uniquely identify each oligomer in the library by determining ... the location of the oligomer on the VLSIPS^{TM} chip." (see Dower et al, columns 2-3, lines 64-67), which reads on claim 38 wherein "said solid support is ... a flat platform" since a VLSIPS^{TM} chip is a flat platform and also represents a "single" solid support.

For **claim 39**, Dower et al teaches "one can uniquely identify each oligomer in the library by determining ... the location of the oligomer on the VLSIPS^{TM} chip." (see Dower et al, columns 2-3, lines 64-67).

For **claim 40**, Dower et al teaches "one can uniquely identify each oligomer in the library by determining ... the location of the oligomer on the VLSIPS^{TM} chip." (see Dower et al, columns 2-3, lines 64-67), which reads on claim 40 wherein "said flat platform is ... a chip" because VLSIPS^{TM} chips can have a "plurality of locations" spaced at any distance and are addressable because "one can uniquely identify each oligomer in the library" on the chip. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For **claim 44**, Dower et al teaches that "glass" beads can be used as a solid support. (see Dower et al, columns 23, lines 62-67), which reads on claim 44 wherein "said solid support is ... glass."

For **claim 45**, Dower et al does not provide a specific example of an oligosaccharide with at least two contiguous saccharide units. However, Schuster et al teaches a branched tetrasaccharide with two covalently linked saccharide units (see Schuster et al, page 1136, scheme 1, compound 6).

For **claim 46**, Dower et al does not provide a specific example of a branched oligosaccharide. However, Schuster et al teaches a branched tetrasaccharide (see Schuster et al, page 1136, scheme 1, compound 6).

For **claim 47**, Dower et al does not provide a specific example of an oligosaccharide wherein "at least one of said plurality of said at least one branch is formed of identical core and branching saccharide units. However, Nicolaou et al teaches a branched dodecasaccharide with identical core and branching units (see Nicolaou et al, page 1560, scheme 2, compound 15).

For **claim 48**, Dower et al does not provide a specific example of an oligosaccharide with at least four saccharide units. However, Schuster et al teaches a branched tetrasaccharide (see Schuster et al, page 1136, scheme 1, compound 6).

For **claim 49**, Dower et al does not provide a specific example of an oligosaccharide with at least five saccharide units. However, Nicolaou et al teaches a branched dodecasaccharide (see Nicolaou et al, page 1560, scheme 2, compound 15).

For **claim 50**, Dower et al does not provide a specific example of an oligosaccharide with at least six saccharide units. However, Nicolaou et al teaches a branched dodecasaccharide (see Nicolaou et al, page 1560, scheme 2, compound 15).

For **claim 51**, Dower et al does not provide a specific example of an oligosaccharide with at least seven saccharide units. However, Nicolaou et al teaches a branched dodecasaccharide (see Nicolaou et al, page 1560, scheme 2, compound 15).

For **claim 53**, Dower et al teaches the carbohydrate libraries that represent naturally occurring complex carbohydrates (see Dower et al, column 1, line 17; and see

also Glossary, column 6, paragraph 3, lines 27-31) (oligomers are "formed from the ... **enzymatic** addition of monomer subuits. Such oligomers include ... ***linear*, cyclic, and branched polymers** of ... polysaccharides", which would include naturally occurring complex carbohydrates) (see also Dower et al, column 7, lines 57).

For **claim 54**, Dower et al teaches that the complex combinatorial libraries may be "useful in therapeutic treatments such as for autoimmune diseases" (see Dower et al, column 7, lines 57), which reads on claim 54 wherein "said natural complex carbohydrates are associated with ... autoimmune disease."

For **claim 55**, Dower et al teaches that the complex combinatorial libraries may be composed of ligands that serve as the "natural ligand" to which the receptor binds and the receptors include proteins in human diseases including autoimmune diseases (see Dower et al, column 7, lines 57; see also column 6, line 8).

For **claim 56**, Dower et al teaches that the complex combinatorial libraries may be composed of ligands that serve as the "natural ligand" to which the receptor binds and the receptors include proteins in human diseases including autoimmune diseases (see Dower et al, column 7, lines 57; see also column 6, line 8), which reads on claim 56 wherein "said human source is selected from the group consisting of a tissue, cells and body fluids" because antibodies and their corresponding antigens are found in tissue, cells and body fluids. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the

applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For **claim 57**, Dower et al teaches that the complex combinatorial libraries may be composed of ligands that serve as the "natural ligands" to which the receptor binds and the receptors include proteins in human diseases including autoimmune diseases (see Dower et al, column 6, line 8).

For **claim 58**, Dower et al teaches that the complex combinatorial libraries may be composed of ligands that serve as the "natural ligand" to which the receptor binds and the receptors include proteins in human diseases including autoimmune diseases (see Dower et al, column 7, lines 57; see also column 6, line 8).

It would have been prima facia obvious to one having ordinary skill in the art at the time the invention was made to build complex carbohydrate libraries as taught by Nicolaou et al with enzymes as taught by Schuster et al to screen for complex carbohydrate binding entities as taught by Dower et al because Dower et al explicitly states that "enzymes" can be used to synthesize carbohydrate libraries for screening and that these carbohydrate libraries can be "complex" (see Dower et al, column 1, line 17; and see also Glossary, column 6, paragraph 3, lines 27-31) (oligomers are "formed from the ... **enzymatic** addition of monomer subuits. Such oligomers include ... ***linear, cyclic, and branched polymers*** of ... polysaccharides") (emphasis added). Furthermore, one of ordinary skill in the art would have been motivated to use the invention of Dower et al in a manner as taught by Nicolaou et al and Schuster et al because a larger variety of complex carbohydrates with potentially stronger binding

affinity can be screened (see Nicolaou et al, page 1559, first paragraph) (emphasizing the need for "large and diverse libraries of oligosaccharides"). In addition, an elaborate array of protecting/deprotecting groups is not required for enzymatic synthesis. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Nicolaou shows that libraries with large complex carbohydrates can be made and Schuster et al shows that you can link carbohydrate monomers attached to polymers using enzymes.

Response to Arguments

13. Applicant's arguments have been fully considered but they are not found persuasive. The Examiner's rationale is set forth below (Please note that the above rejection has been modified from it original version in Paper No. 6 to more clearly address applicants' newly amended and/or added claims).

Applicants argue that [1] "the teachings of Dower et al., Nicolaou et al. and Schuster et al. alone or in combination do not suggest or describe libraries which are bound to a single support" and further argue that the previous teachings do not provide "any motivation" to seek new carbohydrate library configurations or "any reasonable expectation of success" (see Paper No. 9, page 13, paragraph 3; see also page 14, paragraph 4; see also page 15, paragraph 2; see also page 16, paragraph 3); [2] Chi-Huey Wong did not mention this in his review and therefore the "concept of addressable complex carbohydrate libraries was not known" and that applicants subsequently received awards for presentations in this area (see

Paper No. 9, page 16, paragraph 5; see also pages 16-17); [3] the "lack of commercial glycosyltransferases further indicates the general lack of interest in enzymatic synthesis of complex carbohydrates", which presumably enhances the argument that applicants invention was novel and unobvious; [4] a declaration from Prof. Nathan Sharon states that the invention is "unobvious and patentable" over the prior art (see Paper No. 9, page 17, paragraph 4); [5] prior art libraries were typically constructed for the sole purpose of finding carbohydrate ligands to specific molecules (e.g., lectin), and as such, such libraries are less suitable for the intended purposes listed above since they are less suitable for high throughput screening or profiling" (see Paper No. 9, page 14, paragraph 2); [6] the prior art does not mention or suggest enzymatic synthesis in order to construct an addressable library of carbohydrates on a single solid support and any conditions other than the use of enzymatic synthesis would be to harsh to make the desired addressable library (see Paper No. 9, page 15, paragraphs 2-3).

The Examiner contends that [1] Dower et al does teach "an addressable single support-bound complex carbohydrate library" wherein said single support constitutes and addressable chip as stated in the rejection of record and thus provides motivation for making an addressable carbohydrate-chip and a reasonable expectation of success (see Dower et al, see columns 2-3, bridging paragraph; see also column 12, paragraph 3); [2] the fact that Chi-Huey Wong allegedly did not know about or did not decide to write about addressable complex carbohydrate libraries in this one review does not mean that the concept

was not known i.e., even a comprehensive review cannot cover every topic in the field (see outstanding prior art rejections); [3 and 6] the newly amended claims no longer refer to the "enzymatic synthesis" of complex carbohydrate libraries i.e., the word "enzymatically" has been removed from claim 30; [4] Professor Nathan Sharon is a highly respected member of the scientific community and his comments have been fully considered. However, the test for patentability as outlined in the MPEP does not allow for a declaration to overcome a 35 USC §102(b) or 35 USC §103(a) prior art rejection if a prima facie case has been properly established by the Examiner; [5] the Examiner argues that the teachings of Dower et al does provide for high throughput screening via VLSIPS chips (see Dower et al, see columns 2-3, bridging paragraph; see also column 12, paragraph 3).

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 30-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. In newly amended claim 30 (see Paper No. 9), to the extent that the phrase "synthesizing an addressable complex carbohydrate structures" extends beyond the previous limitation "enzymatically" synthesizing a plurality of complex carbohydrate structures, the increased breadth of possible modification constitutes new matter, since there is no specification support or original claim support for the full scope of the modification; nor has applicant provided any indication where such support exists for the full scope of the modification. Specifically, the Examiner does not find support for "synthesizing" a complex carbohydrate library via any other means than enzymatic synthesis. If applicant believes this rejection is in error, applicant must disclose where in the specification support for the full scope of this modification can be found. As a result, claims 1-2 represent new matter. Therefore, claim 30 and all dependent claims wherein the scope of the claims have been broadened by this amendment are rejected under 35 U.S.C. 112, first paragraph i.e., claims 30-58.

B. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER). Claim(s) 31 was amended (including all dependent claims) and/or added in Paper No. 9. However, applicant did not show where support for these amendment(s) and/or addition(s) can be found in the specification. Specifically, the current amendment for claim 31 states that the "said linker includes at least two covalently linked monomers." There is no support

in the claims or specification for an amino acid that is "inactive." Applicant is required to disclose where in the specification support for the amendment(s) and/or new claims is located. If applicant believes this rejection is in error, applicant must disclose where in the specification support for labeling an "inactive" amino acid can be found. As a result, claim 31 and all claims from which 31 depends represent new matter.

C. In newly amended claim 52-53 (see Paper No. 9), to the extent that the phrase "said plurality of complex carbohydrate structures represent non-naturally [or "naturally" in claim 53] occurring complex carbohydrates" extends beyond the previous limitation "wherein said plurality of complex carbohydrate structures are a representation", the increased breadth of possible modification constitutes new matter, since there is no specification support or original claim support for the full scope of the modification; nor has applicant provided any indication where such support exists for the full scope of the modification. If applicant believes this rejection is in error, applicant must disclose where in the specification support for the full scope of this modification can be found. As a result, claims 52-53 represent new matter. Therefore, claim 52-53 and all dependent claims wherein the scope of the claims have been broadened by this amendment are rejected under 35 U.S.C. 112, first paragraph.

D. In newly amended claim 58 (see Paper No. 9), to the extent that the phrase "said plurality of complex carbohydrate structures represent domains of at least one naturally occurring complex carbohydate" extends beyond the previous limitation "said plurality of complex carbohydrate structures are a representation of domains of at least one natural complex carbohydrate", the increased breadth of possible modification constitutes new

matter, since there is no specification support or original claim support for the full scope of the modification; nor has applicant provided any indication where such support exists for the full scope of the modification. If applicant believes this rejection is in error, applicant must disclose where in the specification support for the full scope of this modification can be found. As a result, claims 52-53 represent new matter. Therefore, claim 52-53 and all dependent claims wherein the scope of the claims have been broadened by this amendment are rejected under 35 U.S.C. 112, first paragraph.

15. Claims 30-58 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claim 30 outlines steps for "synthesizing a plurality of complex carbohydrate structures" to produce an addressable complex carbohydrate library on a single solid support. The scope of these claims includes an infinite number of methods (both enzymatic and now non-enzymatic methods, see New Matter rejection above) for producing an infinite number of complex carbohydrates (i.e., both "naturally occurring" and "non-naturally occurring") wherein no distinguishing structural attributes are provided for the library members (i.e., no structural features are provided for the "naturally

occurring" or "non-naturally occurring" carbohydrates) and no limitations are provided for how said library members are to be synthesized and attached to the solid support. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to make the addressable complex carbohydrate library members on the single solid support. Although the specification discloses several hypothetical examples wherein "enzymes" have been used to synthesize carbohydrates on a single solid support (see Specification, Examples), the specification and claims do not provide ***any*** guidance as to what distinguishing features ***all*** of these methods might share to produce the infinite number of both "natural" and "non-natural" complex carbohydrates that would be hypothetically produced (see also 35 U.S.C. 112, second paragraph rejection on "naturally" and "non-naturally occurring" complex carbohydrates showing that the metes and bounds of the claimed invention cannot be determined). Consequently, it is not possible to determine *a priori* which methods would be encompassed by Applicants newly amended claims because there is no common attributes (i.e., the claims are no longer drawn to the "enzymatic" synthesis of carbohydrate-chips) that can link together ***all*** of these potential methods i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of methods that should be included in this genus from the few examples provided by applicants (i.e., Applicants have only provided examples for enzymatic synthesis) and there is no teaching that would allow a person of skill in the art to determine a priori all the different types of compounds that should be included in the "non-naturally occurring" complex carbohydrates or "naturally occurring" complex carbohydrates.

Especially with regard to method steps for synthesizing the "non-naturally occurring" complex carbohydrates, Applicants' attention is directed to the Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure , formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Friers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)]. If a written description is not provided for a claimed genus of compounds than a written description is not provided for a method of synthesizing or using the claimed genus of compounds because the method steps depend on the compounds which are being produced and are as of yet undefined.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant (i.e., there would be an infinite number of non-enzymatic methods for producing an infinite number of both "natural" and "non-natural" complex carbohydrates on a single solid support), listing examples of enzymatic synthesis (see specification, Catalysts, pages 6-8) is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. **Claims 30-58** are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: reciting positive method steps for "synthesizing" a plurality of complex carbohydrate structures.

17. For **claims 52-58**, the terms "naturally occurring" and "non-naturally occurring" is vague and indefinite because a person of skill in the art could not determine whether a sample was "naturally" occurring or "non-naturally" occurring in ***all*** cases without a specific teaching for every single example (i.e., a person of skill in the art could not determine whether a sugar was "natural" or "non-natural" just by examining its structure) and a specific teaching cannot be provided for every possible sample because this would include an infinite number of samples. Furthermore, it is not clear how much "variation" a "non-naturally occurring" carbohydrate may vary and still be considered a "non-naturally occurring" carbohydrate. Consequently, the metes and bounds of the claimed invention cannot be determined. Therefore, claims 52-58 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 30-32, 35, 38-45, 52-54 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor et al (U.S. Patent No. 5,424,186) (Date of Patent is **June 13, 1995**).

For ***claims 30 and 64***, Fodor et al (see entire document) discloses a method for the light directed spatially addressable "synthesis and use of diverse polymer sequences on a substrate" (see Fodor, column 2, lines 32-33), which anticipates claim 30. For example, Fodor et al discloses the production of complex polysaccharides on an addressable VLSIPS chip using enzymatic synthesis (see Fodor et al, columns 68-69, Section V B, see especially column 69, paragraph 2).

For ***claims 31-32 and 35***, Fodor et al discloses the use of linkers with at least two covalently linked monomers (see Fodor et al, column 2, lines 35-48; see also column 49, Linker section; see also columns 68-69, Section V B, see especially column 69, paragraph 2; see also Figures, especially 40a-e and 41). Fodor et al also discloses light cleavable linkers that would not affect the structure of the carbohydrate when cleaved and would allow the attachment of any group, which would include p-nitrophenyl, amine or squaric acid derivatives (see Fodor et al, column 15, lines 55-65). Furthermore, Fodor et al teaches the linkers can be of any length for

For ***claims 38-40***, Fodor et al discloses the use of a chip, which would anticipate a flat platform (see Fodor et al, columns 68-69, Section V B, see especially column 69, paragraph 2; see also column 9, lines 20-28; see also column 14, last paragraph) and can have a plurality of discrete locations concentrations as high as 108 different monomers per chip (see Fodor et al, figures 1-7; see also column 19, lines 45). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 41-44***, Fodor et al discloses that "any conceivable substrate may be employed" (see Fodor et al, column 14, last paragraph; see also column 15). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 45 and 52-53***, Fodor et al discloses that the carbohydrate polymers can be made from any number of monomers to make any sequence, which would include both "natural" and "non-natural" complex carbohydrates and would also include those

found in human cells including cells derived from tissue cells and body fluids (see Fodor et al, columns 68-69, Section V B, see especially column 69, paragraph 2; see also column 2, last two paragraphs; see also figure 26) (see Fodor et al, column 3, paragraph 1, "Other possible applications of the inventions herein include diagnostics in which various antibodies for a particular receptors would be placed on a substrate and, for example, blood sera would be screened for immune deficiencies"; see also column 6, section 7 describing the definition of a receptor to include polysaccharides i.e., complex carbohydrates; see also column 13, lines 36-39; see also figure 34), which would encompass the limitations in claims 45-53 and 55-57. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 54***, Fodor et al discloses the use of the that the complex carbohydrates can be associated with autoimmune disease (see Fodor et al, column 3, paragraph 1, "Other possible applications of the inventions herein include diagnostics in which various antibodies for a particular receptors would be placed on a substrate and, for example, blood sera would be screened for immune deficiencies"; see also column 6, section 7 describing the definition of a receptor to include polysaccharides i.e., complex carbohydrates; see also column 13, lines 36-39; see also figure 34).

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 30-58 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fodor et al (U.S. Patent No. 5,424,186) (Date of Patent is **June 13, 1995**) and Seitz et al (Seitz, O.; Wong, C. H. "Chemoenzymatic Solution- and Solid-Phase Synthesis of O-Glycopeptides of the Mucin Domain of MAdCAM-1. A general Route to O-LacNAc, O-Sialyl-LacNAc, and O-Sialyl-Lewis-X Peptides" *J. Am. Chem. Soc.*, **1997**, *119*, 8766-8776) and Seifert et al (Seifert, J. and Unverzagt, C. "Synthesis of three Biantennary N-Glycans containing the α-1,6 Core-Fucosyl Motif" *Tetrahedron Letters*, **1997**, *38(45)*, 7857-7860.

23.

For ***claims 30-32, 35, 38-45, 52-54 and 64***, Fodor et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 30-32, 35, 38-45, 52-54 and 64 and, consequently, also renders obvious claims 30-32, 35, 38-45, 52-54 and 64.

For **claims 33-34**, Fodor et al does not provide a specific example of a "cleavable" linker for a complex oligosaccharide library (see 35 U.S.C. 102(b) rejection, above). However, Seitz teaches a cleavable linker that does not "harm" the sugar residues (see Seitz et al, page 8772, scheme 12).

For **claims 36-37**, Fodor et al does not provide a specific example of a linker for a complex oligosaccharide library that is at least 20 Angstroms long. However, Seitz teaches the HYCRON linker that is >20 Angstroms long (see Seitz et al, page 8768, scheme 2, showing HYCRON linker).

For **claim 46**, Fodor et al does not provide a specific example of a branched oligosaccharide. However, Seitz et al teaches a branched tetrasaccharide (see Seitz et al, page 1136, schemes 10-12).

For **claim 47**, Fodor et al does not provide a specific example of an oligosaccharide wherein "at least one of said plurality of said at least one branch is formed of identical core and branching saccharide units. However, Seitz et al teaches a branched tetrasaccharide with identical core and branching units (see Seitz et al, page 1136, scheme 10-12).

For **claim 48**, Fodor et al does not provide a specific example of an oligosaccharide with at least four saccharide units. However, Seitz et al teaches a branched tetrasaccharide (see Seitz et al, page 1136, scheme 10-12).

For **claim 49**, Fodor et al does not provide a specific example of an oligosaccharide with at least five saccharide units. However, Seifert et al teaches a branched dodecasaccharide (see Seifert et al, page 7857, figure 1).

For **claim 50**, Fodor et al does not provide a specific example of an oligosaccharide with at least six saccharide units. However, Seifert et al teaches a branched dodecasaccharide (see Seifert et al, page 7857, figure 1).

For **claim 51**, Fodor et al does not provide a specific example of an oligosaccharide with at least seven saccharide units. However, Seifert et al teaches a branched dodecasaccharide (see Seifert et al, page 7857, figure 1).

For **claim 55**, Fodor et al does not provide a specific example of an oligosaccharide wherein "said natural complex carbohydrates are derived from a human source." However, Seitz et al teaches "glycopeptides containing an O-linked sialyl-Lewis-X (Sle^x) tetrasaccharide" (see Seitz et al, page 1136, scheme 10-12).

For **claim 56**, Fodor et al does not provide a specific example of an oligosaccharide wherein "said natural complex carbohydrates are derived from a human source." However, Seitz et al teaches "glycopeptides containing an O-linked sialyl-Lewis-X (Sle^x) tetrasaccharide" (see Seitz et al, page 1136, scheme 10-12), which reads on claim 56 wherein "said human source is selected from the group consisting of ...

cells" because adhesion molecules that express Sle^x are found on the surface of human cells.

For **claim 57**, Fodor et al does not provide a specific example of an oligosaccharide wherein "said plurality of complex carbohydrate structures represent domains of at least one naturally occurring complex carbohydrate." However, Seitz et al teaches "glycopeptides containing an O-linked sialyl-Lewis-X (Sle^x) tetrasaccharide" (see Seitz et al, page 1136, scheme 10-12).

For **claim 58**, Fodor et al does not provide a specific example of an oligosaccharide wherein "said at least one naturally occurring complex carbohydrate is present in human cells." However, Seitz et al teaches "glycopeptides containing an O-linked sialyl-Lewis-X (Sle^x) tetrasaccharide" (see Seitz et al, page 1136, scheme 10-12), which is present in human cells.

It would have been prima facia obvious to one having ordinary skill in the art at the time the invention was made to build complex carbohydrate libraries with branched dodecasaccharides as taught by Seitz et al and Seifert et al using enzymatic synthesis on a chip to "identify carbohydrate-based ligands" as taught by Fodor et al because Seitz et al specifically states that "Glycosyltransferases [i.e., enzymes] have shown to be versatile tools in oligosaccharide [solid-phase] synthesis" (see Seitz et al, page 8767, column 1, first paragraph; see also scheme 12) (showing that enzymes can be used in solid-phase synthesis, which is required for library production using resins) and the invention of Fodor et al also requires the solid-phase synthesis of oligosaccharies (i.e., on a chip) using enzymes (see Fodor et al, columns 68-69, Section V B, see especially column 69,

paragraph 2). Furthermore, one of ordinary skill in the art would have been motivated to use the invention of Fodor et al in a manner as taught by Seitz et al and Seifert et al to because Fodor et al requires the synthesis of diverse sequences of oligosaccharides for screening purposes (see Fodor et al. Summary of invention) and Seifert et al and Seitz provide new methods for increasing the diversity (see Seifert et al, Figure 3) (showing high yielding stereospecific monomer additions). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Seitz et al and Seifert et al teach that large complex oligosaccharides can be synthesized on solid-support using enzymes for "combinatorial access to complex structures" (see Seitz et al, page 8766, column 2, second paragraph).

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

42. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon D. Epperson, Ph.D.
March 25, 2003

BENNETT CELSA
PRIMARY EXAMINER